REMARKS

The Office action dated September 8, 2008 is acknowledged. Claims 1-32 are pending in the instant application. Claims 1-15 and 20-29 have been rejected and claims 16-19 and 30-32 have been withdrawn. By the present Office Action response, claims 1, 3 and 15 have been amended, claim 2 has been cancelled and claims 33-36 have been added. In particular, claim 1 has been amended to clarify certain recitations. For example, the film-shaped administration forms that are produced in accordance with the presently claimed invention are in a dry state, as set forth in claim 1. Therefore, "solvent or solvent mixture" has been deleted to avoid ambiguity. Claim 1 has been additionally amended to clarify that the pH value of the base mass is the pH value which the base mass has when it is exposed to water or an aqueous solvent mixture (see, for example, paragraph [00018] of the specification). The introduction of the term "water or aqueous solvent mixture" into claim 1 is based on claim 2, now cancelled. The phrase "during the production of said administration form" of claim 1 has been transferred to earlier in the claim for clarification purposes. Newly added claims 33 and 34 recite the present invention wherein the active substance is present in salt form, as supported by paragraphs [00016] and [000017] of the present specification. Claim 35 recites the present invention wherein at least one active substance is selected from the group of aroma substances, without a pharmaceutical active substance being included in the administration form, as supported by paragraph [000042] of the specification. Reconsideration is respectfully requested in light of the arguments made herein. No new matter has been added.

Information Disclosure Statement

The Examiner states that no copies of the cited prior art references cited in the

Information Disclosure Statement filed on December 27, 2005 have been submitted for consideration by the Examiner. Copies of the non-U.S. patent references and the non-patent reference are enclosed herewith for the Examiner's consideration. A hard copy of the U.S. published application reference is not required and therefore are not submitted herewith.

Rejection of claims 3 and 15 under 35 U.S.C. 112, second paragraph

The Examiner has rejected claim 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. In particular, the Examiner states that the Markush group of items for the matrix-forming polymer contains the items polyethylene oxide polymers and polyethylene glycol, which are two different names for the same polymer. The Examiner also states that there is a broad recitation of "natural gums" and a more specific recitation of "gum Arabic."

Claim 3 has been amended to delete the terms "gum Arabic" and "polyethylene glycol." In addition, "acrylates" and "tragacanth" have also been deleted from claim 3 since "acrylates" appears to be synonymous with "polyacrylates" and "tragacanth" falls within the broader limitation of "natural gums." Withdrawal of this rejection is requested.

Claim 15 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. In particular, the Examiner states that the claim recites a use of the administration form according to claim 1, but since the claim does not specify any steps involved in the method/process it is unclear what

method/process is intended to be encompassed.

Claim 15 has been amended accordingly. Claim 15 recites a method of transmucosal administration of active substances, support for which may be found in the specification such as at paragraphs [0002], [0005] or [00027]. This method may be employed for the treatment of either humans or animals, support for which may be found in the specification such as at paragraphs [0002], [0005], [00020], [00035], [00039], [00041] or [00055]. In this regard, newly added dependent claim 36 recites the mucosal target sites used in accordance with the method of claim 15, support for which may be found in the specification such as at paragraphs [0007] and [00020]. Withdrawal of this rejection is also requested.

Rejection of claim 15 under 35 U.S.C. 101

Claim 15 has been rejected for reciting a use without setting forth any steps involved in the process. Claim 15 has been amended, as discussed above. Withdrawal of this rejection is respectfully requested.

Rejection of claims 1-5, 7-11, 13-15, 21, 22, 24-26 and 29 under 35 U.S.C. 102(b)

Claims 1-5, 7-11, 13-15, 21, 22, 24-26 and 29 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,572,832 (Kigasawa, et al.). The Examiner states that Kigasawa, et al. disclose every limitation recited in the aforementioned claims, namely, soft buccal compositions which comprise a medicament to be absorbed through the oral cavity, a water-soluble protein, a polyhydric alcohol and a fatty acid ester and/or a carboxyvinyl polymer. The Examiner also believes that the reference discloses a soft buccal comprising the active ingredient pindolol which is prepared using the film forming polymer gelatin (gelatine), pH 6.5 phosphate buffer and

the excipients propylene glycol, medium-chain fatty acid triglycerides, sucrose fatty acid ester, glycerin, mannitol and corn starch (col. 12, lines 43-60; Example 8). The Examiner further states that the total weight of the excipients is about 70% of the total weight of the product and that after sonication to create a dispersion, the gelatin was added and the resulting mixture kneaded and cut into plate-shaped (i.e., a film-shaped) dosage form, which took between 16 minutes and 17 minutes - 15 seconds to disintegrate. The Examiner thus concludes that Kigasawa, et al. teach a film-shaped, dried dosage form comprising an active ingredient and at least one matrix-forming polymer whose pH value is adapted to the physiological pH value of the mucosa to which the administration form is to be applied.

The Applicants respectfully disagree with the Examiner's conclusion and submit that the present invention as defined in the present claims is patentably distinct from the invention disclosed in the prior art Kigasawa, et al. reference. In particular, the Examiner refers to Kigasawa, et al. for the teaching that a "phosphate buffer (pH 6.5)" (col. 8, line 44) was used. However, this is the only passage in Kigasawa, et al. where the pH is mentioned at all. In this regard, the Applicants respectfully disagree that Kigasawa, et al. teach film-shaped administration forms having a base mass adjusted to a physiological pH value as presently claimed. First, it should be noted that Example 8 Kigasawa, et al. includes two different manufacturing methods which result in different dosage forms and which are designated as (a) and (b), respectively. Only in version (b) of Example 8 (col. 12, lines 43-60) is a phosphate buffer of pH 6.5 used. Although Kigasawa, et al. do not indicate any reason why this particular buffer was used in Example 8(b), it appears that this buffer was selected in order to obtain a "pre-mix" containing active substance

(pindolol) admixed with other ingredients, such as propylene glycol, fatty acid triglyceride, lecithin and sucrose fatty acid ester. The pre-mix is then added to a mixture of gelatin, glycerin and mannitol in order to produce a gel. In contract to version (a) of Example 8, version (b) does not include a drying step. Therefore, the resulting "plate-shaped soft buccal" is in fact a gelled composition (emphasis added) comprising a substantial amount of water (or buffer). In contrast, present claim 1 require the administration form to be "a dried film." Example 8 of Kigasawa, et al. does not pertain to a dried film at all.

The Applicants further submit that present claim 1 specifies that the pH of the base mass is adjusted to a physiological pH value during production. In Example 8 of Kigasawa, et al., the matrix-forming polymer of the base mass is gelatin. However, the pH value of 6.5 is only specified for the active-substance containing "pre-mix" (including other ingredients, such as fatty acid triglyceride) which does not yet contain the matrix-forming polymer glycerin. This polymer is added only in the subsequent process step, together with glycerin and mannitol (Office action, page 7, last three lines – "After sonification to create a dispersion, the gelatin was added ..."). Therefore, it is submitted that the pH of the resulting mixture, which also includes the base polymer, remains unknown. Kigasawa, et al. simply fail to teach a base mass adjusted to a physiological pH value in accordance with the presently claimed invention.

In turn, since Kigasawa, et al. specify only the pH (6.5) and the amount (11.75 g) of the phosphate buffer, but not its concentration, the buffer capacity of this buffer is unknown. Due to the presence of gelatin and lecithin, which substances are known to affect the pH of a solution, it is speculative whether the use of a phosphate buffer of pH

6.5 and unknown concentration will have the effect of adjusting the pH of the gelatin-containing base mass described by Kigasawa, et al. to a physiological pH value. Furthermore, Kigasawa, et al. fail to provide any teaching indicating that the use of "phosphate buffer (pH 6.5) may have such effect. Therefore, Kigasawa, et al. simply cannot be interpreted as disclosing a base mass which is adjusted to a physiological pH value as set forth in the present claims.

In conclusion, it is submitted that Kigasawa, et al. fail to teach each and every limitation of the present claims, and therefore fail to anticipate the present invention as set forth in the present claims. Withdrawal of this rejection is respectfully requested.

Rejection of claims 1-15 and 20-29 under 35 U.S.C. 103(a)

Claims 1-11, 13-15 and 20-29 have been rejected as being unpatentable over Kigasawa, et al. The Examiner states that Kigasawa, et al. disclose soft buccal compositions which comprise a medicament to be absorbed through the oral cavity, a water-soluble protein, a polyhydric alcohol and a fatty acid ester and/or a carboxyvinyl polymer. The Examiner also states that forms include sheets, bands and disks. The Examiner further states that the reference discloses a soft buccal comprising the active ingredient pindolol which is prepared using the film forming polymer gelatin (gelatine), pH 6.5 phosphate buffer and the excipients propylene glycol, medium-chain fatty acid triglycerides, sucrose fatty acid ester, glycerin, mannitol and corn starch. The Examiner still further states that the total weight of the excipients is about 70% of the total weight of the product and that after sonication to create a dispersion, the gelatin was added and the resulting mixture kneaded and cut into plate-shaped (i.e., a film-shaped) dosage form, which took between 16 minutes and 17 minutes, 15 seconds to disintegrate. The

Examiner thus concludes that Kigasawa, et al. teach a film-shaped, dried dosage form comprising an active ingredient and at least one matrix-forming polymer whose pH value is adapted to the physiological pH value of the mucosa to which the administration form is to be applied.

The Examiner states that Kigasawa, et al. fail to explicitly prepare administration forms which contain aroma substances or cellulose derivatives or an administration form which disintegrates in less than 10 minutes. However, the Examiner argues that Kigasawa, et al. does disclose that additives can be added in addition to the required ingredients, including flavorings (i.e., aroma substances), such as menthol, lemon oil and citrus flavors, as well as other excipients, disintegrating adjusting agents, emulsifiers, dispersants, binders and thickeners. Additionally, the Examiner states that the reference discloses that for the required polyhydric alcohol component, ingredients can be ethylene glycol, propylene glycol or polyethylene glycol, and that included in the category of polyhydric alcohols are cellulose and cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and carboxymethyl cellulose.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a dosage form with an aroma ingredient, taught by Kigasawa, et al., as an ingredient to impart a flavor/aroma to the medicament and to use a cellulose derivative such as ethyl cellulose for the required polyhydric alcohol component of the film administration. The Examiner also states that the amount of an aroma ingredient in a composition is clearly a result effective parameter that one skilled in the art would routinely optimize, and the aroma/flavor chosen and the strength of the aroma/flavor desired or required in the composition, such as to mask the taste of a

bitter active ingredient, would determine the amount of the ingredient present in the composition. The Examiner further states that one skilled in the art would adjust the composition of the tablet in order to provide a fast disintegration of the dosage form to minimize the possibility for swallowing the dosage form and losing the benefits of the buccal administration form.

Claims 1-15 and 20-29 have been rejected as being unpatentable over Kigasawa, et al., as applied to claims 1-11, 13-15 and 20-29 above, and further in view of U.S. Patent No. 5,900,247 (Rault, et al.). The Examiner states that Kigasawa, et al. disclose soft buccal administration forms of active ingredients that can be formulated as disks or wafers, as discussed above. However, the Examiner states that Kigasawa, et al. fail to disclose a multilayer dosage form.

The Examiner refers to Rault, et al. and states that the reference discloses a bioadhesive pharmaceutical composition to locally release active ingredients through various mucosal membranes, and that the bioadhesive composition comprises a vinyl acetate/polyvinylpyrrolidinone copolymer, at least one active ingredient, optionally a cellulose or cellulose derivative such as ethyl cellulose or hydroxypropylmethyl cellulose and excipients such as plasticizers, flavoring agents or sweeteners. The Examiner further states that after spreading of the bioadhesive mixture onto a biodegradable or non-biodegradable protective film or substrate, the assembly is dried and the protective film is chosen for its adhesive or bioadhesive properties and is peelable. According to the Examiner, this process results in the production of a multilayered administration form and that in Example 4 of the reference, a composition is prepared which contains approximately 3% by dry weight of flavoring agents.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a buccal administration form as taught by Kigasawa, et al. and to place this material on a protective film as taught by Rault, et al., resulting in a multilayered administration form. The Examiner also concludes that Rault, et al. provide additional guidance to one skilled in the art as to the amount of flavoring ingredients, which can include aroma substances, that can be added to such compositions.

It is respectfully submitted that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The Applicants respectfully submit that one skilled in the art would have no suggestion or motivation to combine the aforementioned references in order to arrive at the present invention. Additionally, even if one skilled in the art were to consider the teachings of the cited prior art alone or in combination, each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered.

The Applicants first respectfully disagree with the Examiner's position for at least the numerous deficiencies of Kigasawa, et al. set forth above, namely, the failure of Kigasawa, et al. to recognize the importance of adjusting the pH of the matrix-forming polymer-containing base mass to a physiological pH which is the physiological pH value of the mucosa to which the administration form is to be applied. As discussed above, the recitation of "phosphate buffer (pH 6.5)" in Kigasawa, et al.'s Example 8 is not made in

connection with a polymer-containing base mass and Kigasawa, et al. fail to provide any teaching or suggestion that the matrix polymer-containing base mass (i.e., gelatin-containing) should be adjusted to a physiological pH value. Therefore, the Applicants disagree with the Examiner's statement on page 8 (second paragraph) of the Office action which alleges that "Kigasawa, et al. teaches a film-shaped, dried dosage forms comprising an active ingredient and at least one matrix-forming polymer whose pH value [is] adapted to the physiological pH..."

In addition, the Applicants submit that Example 8 of Kigasawa, et al. only discussed pH in connection with a gel (emphasis added) composition, but not in connection with a dried film as set forth in the present claims. On the other hand, Example 8(a) of Kigasawa, et al., which does relate to a dried composition (col. 12, lines 36-37), the addition of phosphate buffer pH 6.5 is not considered at all. Therefore, considering the differences between Examples 8(a) and 8(b) of Kigasawa, et al., one skilled in the art would have assumed that according to the teachings of Kigasawa, et al. addition of phosphate buffer having pH 6.5 is only required when producing gelled "soft buccals" as described in Example 8(b) but not when producing dried pieces as described in Example 8(a). There is no teaching at all that the phosphate buffer with pH 6.5 of Example 8(b) can be applied to Example 8(a), nor would there be any reasonable motivation to do so. Kigasawa, et al. simply fail to teach or suggest a dried film comprising a base mass adjusted to a particular physiological pH value.

The Examiner, when referring to Example 8, has combined the alternative descriptions of Example 8(a) and Example 8(b), although these two Examples relate to different compositions. Example 8(a) relates to a dried product whereas Example 8(b)

relates to a non-dried gel product, and the use of a pH-adjusted phosphate buffer is only described in Example 8(b) but not in Example 8(a). Therefore, the Applicants submit that these two differing teachings would not be combined by one skilled in the art to arrive at a new and completely different teaching which is not specifically taught or disclosed at all by Kigasawa, et al.

With reference to page 7 of the Office action, last paragraph, it is pointed out that the dosage form described in Kigasawa, et al.'s Example 8(b) disintegrates within 16 minutes (as disclosed in present claim 11). However, it is again submitted that this Example relates to a gel composition whereas the present claims recite dried films. On page 8 of the Office action (first paragraph), the Examiner refers to the disintegration times disclosed in Example 8(a). However, this Example does not include a pH-adjusted base mass, which is also in contrast to the presently claimed invention. Therefore, it is submitted that the recited Examples regarding disintegration times do not correlate at all to the presently claimed invention.

With respect to new claims 33 and 34, it is further submitted that the prior art fails to teach or suggest pH adjustment in the case where salts of pharmaceutically active substances are used. Example 8 of Kigasawa, et al. employs the active substance pindolol, but which is not used in salt form. As set forth in the present invention, pH adjustment during production of the claimed administration forms is particularly advantageous in cases where the active substance is present in salt form (see, for example, the present specification paragraphs [00016], [00017], [00023]; page 10, Table 1: "active substance hydrochloride", (paragraph [00056])).

As set forth in the Office action, the Examiner refers to Rault, et al. for the sole

reason of teaching multilayer dosage forms. Clearly, Rault, et al. fail to make up for any of the numerous aforementioned deficiencies of Kigasawa, et al. and therefore the combination with Kigasawa, et al. would fail to teach or disclose each and every limitation of the presently claimed invention. Therefore, the Applicants respectfully request that this obviousness rejection be withdrawn.

Conclusion

For the foregoing reasons, it is believed that the present application, as amended, is in condition for allowance, and such action is earnestly solicited. Based on the foregoing arguments, amendments to the claims and deficiencies of the prior art references, the Applicants strongly urge that the obviousness-type rejection and anticipation rejections be withdrawn. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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